1. The Specification Objections

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. According to the Examiner, Claim 15 recites "SSeCKS polypeptide that has an increased affinity for cyclin D"; however the only variants of SSeCKS recited in the specification have a decreased affinity for cyclin D. In this regard, Applicants respectfully invite the Examiner's attention to page 33, lines 3-11, of the specification which disclose variants of SSeCKS other than those having a decreased affinity for cyclin D.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants have amended the specification to delete the embedded hyperlink.

Additionally, the disclosure is objected to because Figure 54 (top line) discloses an amino acid sequence which is not identified by the appropriate SEQ ID NO in the "Brief Description" of the Figure. Applicants have amended the specification to insert the appropriate SEQ ID NO.

2. The Rejections Under 35 U.S.C. § 112 Should Be Withdrawn

Claims 13, 14 and 15 are rejected under 35 U.S.C. § 112, first paragraph. Claim 14 is directed to a method of using a nucleic acid molecule that encodes a SSeCKS polypeptide fused to a "cytoskeletal anchoring peptide." The Examiner alleges that the specification does not describe or identify any "cytoskeletal anchoring peptide."

Applicants assert that such cytoskeletal anchoring peptides are known in the art therefore it is not necessary to disclsoe such peptides. In this regard, the Examiner's attention is

directed to page 40, lines 10-11 of the specification, which references two publications describing anchoring domains.

Claim 15 is directed to a method of using a nucleic acid molecule that encodes a SSeCKS polypeptide that has an increased affinity for cyclin D. However, the Examiner maintains that the specification makes no mention of such a nucleic acid or polypeptide.

Applicants assert that the instant specification as filed discloses (i) the SSeCKS nucleotide sequence (see p. 12, lines 26-28 of the specification); (ii) the region of the SSeCK protein involved in cyclin D binding, *i.e.*, the CY domain; and (iii) methods for assaying binding of cyclin D to SSeCK (see, Section 14.1.9 of the specification). Applicant maintains that given the specific teachings of the specification, one skilled in the art could, without undue experimentation, identify SSeCK polypeptides withincreased binding affinity for cyclin D.

Claim 13, 14 and 15 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method for inhibiting cell proliferation in cultured cells, does not reasonably provide enablement for inhibiting cell proliferation *in vivo*. According to the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In this regard, Applicants refer to the Rule 132 Declaration of Dr. Irwin Gelman (the "Gelman Declaration") submitted in related application Serial No. 08/978277 to support *in vivo* applications. As described in the Gelman Declaration experiments were conducted in which prostate tumor cancer cells were transfected with either a control recombinant expression vector

or a recombinant expression vector containing the SSeCKS gene under the control of an inducible promoter, i.e., the tetracycline (tet) inducible promoter (¶4, Gelman Declaration). Following transfection, the prostate cancer cells were injected into athymic nude mice (¶5, Gelman Declaration). As indicated by the data presented, the induced expression of SSeCKS was capable of reducing *in vivo* proliferation of tumor cells and the formation of lung metastases (¶6, Gelman Declaration). A correlation between loss of SSeCKS expression *in vivo* and the onset of tumorigenesis is further supported by the observation that the putative human SSeCKS orthologue has been mapped and has been shown to be deleted in a significant proportion of advanced human prostate cancer (¶8, Gelman Declaration).

Applicant Gelman demonstrated (i) the successful transfer of a nucleic acid molecule encoding an SSeCKS protein into a tumor cell, and (ii) that the expression of the SSeCKS protein is sufficient to inhibit *in vivo* proliferation of the tumor cells and reduce the formation of metastases. Thus, Applicant Gelman asserts that the instant specification is fully enabled for the pending claims.

Claim 14 is rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. Applicants have amended claim 14 to indicated that cytoskeltal anchoring peptide is linked to the encoded SSeCKS polypeptide.

Claim 15 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "increased affinity" in claim 15 is a relative term which

renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. There is no referent by which "increased" can be determined. Applicants have amended the claim to encompass "a method of inhibiting cell proliferation in a cell comprising introducing a nucleic acid molecule encoding a SSeCKS polypeptide that has an increased affinity for cyclin D ***as compared to a wild type SSeCKS polypeptide***."

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2. The Claims Are Not Anticipated

Claim 13 is rejected under 35 U.S.C. §102(a) and (b) as being clearly anticipated by Lin et al. (Mol. Cell. Biol. 15 (5): 2754-2762, May 1995) or Lin et al.(Cancer Res. 57(11): 2304-2312, 01 June 1997) .

Lin et al. (1995) discloses a method of inhibiting proliferation of *src*-transformed NIH 3T3 cells by transfection with a plasmid expressing the truncated SSeCKS polypeptide (SEQ ID NO: 2). Lin et al. (1997) discloses a method of inhibiting proliferation of conditionally *src*-transformed NIH 3T3 cells by transfection with a plasmid expressing the full-length rat SSeCKS polypeptide (SEQ ID NO: 4) and growth in low calf serum media.

Applicants have amended claim 13 to encompass "a method of inhibiting cell proliferation in a cell comprising introducing a nucleic acid molecule encoding a SSeCKS polypeptide ***comprising a CY domain that is capable of binding cyclin D and preventing translocation of cyclin D into the nucleus***. Applicants maintain that neither of the Lin references describes binding of SSeCKS to cyclin D, much less the region of SSeCK responsible

for such binding. Therefore, the presently claimed invention can not be anticipated by Lin (1995) or Lin (1997).

CONCLUSION

Entry of the foregoing amendments and remarks into the file history of the above-identified application is respectfully requested. Applicant believes that the foregoing amendments and remarks place the claims in condition for allowance. Withdrawal of all rejections and reconsideration of the amended claims is requested.

Applicant submit herewith as attached APPENDIX A, a marked up version of the specification to show all changes relative to the previous version of the specification.

Respectfully submitted,

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IN THE SPECIFICATION

Please amend the specification as follows:

Delete the brief description of Figure 54 and insert the following brief description:

FIGURE 54. Sequence similarity between SSeCKS (SEQ ID NO:4) and the Abl-binding domain in pRb. Identical a.a. residues (vertical lines) or similarly charged residues (colons) are shown for the SSeCKS and newt Rb (Genbank accession # Y09226) proteins.

On page 89, replace the last paragraph that continues on page 90, with the following paragraph:

Mapping of SSeCKS, as referred to herein as Gravin. Rodent SSeCKS and human Gravin/AKAP12 show 83% identity over the first ~1000 a.a., <20% similarity over the next ~500 a.a., and identity in two 15-a.a. stretches at the C-termini, one of which encodes a PKA anchoring site (Nauert et al., 1997, Curr. Biol. 7:52-62). Full-length SSeCKS cDNA recognizes Gravin mRNA under conditions of stringent hybridization (Gelman et al., 2000, Histochem. J. 32:13-26). Using a Gravin cDNA probe, human gravin was mapped by fluorescence in situ hybridization (FISH) to chromosome 6q24-25.2 (Fig. 43). These map coordinates are confirmed by microsatellite markers (Sanger Sequencing Centre, UK). Secondary hybridization signals were not detected which might reflect a second family member. FISH analysis using a full-length SSeCKS cDNA probe identified the same, singular region. Moreover, mouse SSeCKS maps to the Tsga12 locus at the centromeric end of chromosome 10p, which is syntenic with human chromosome 6q24-27[4] [(Mouse Genome Informatics Web Site; http://www.informatics.jax.org/)], strongly suggesting that SSeCKS and Gravin/AKAP12 are orthologues. Deletions in this region are associated with advanced, non-organ confined prostate

cancer cases (Isaacs, et al., 1994, Quant. Biol. 59:653-659; Nupponen et al., 1998, Cancer Genet. Cytogenet. 101:53-57; Alers et al., 2000, Lab. Investig. 80:931-942; Crundwell et al., 1996, Int. J. Cancer 69:295-300; Bookstein, et al., 1997, Br. J. Urol. 79(Suppl 1):28-36; Srikantan et al., 1999, Int. J. Cancer 84:331-335; Visakorpi, T., 1999, Ann. Chir. Gynaecol. 88:11-16; Cunningham et al., 1996, Cancer Res. 56:4475-4482; Cooney et al., 1996, Cancer Res. 56:4150-4153; Visakorpi et al., 1995, Cancer Res. 55:342-347), indicating a possible role for SSeCKS/Gravin in prostate oncogenesis.

IN THE CLAIMS:

Please amend the claims as follows:

13. (amended) A method of inhibiting cell proliferation in a cell comprising introducing a nucleic acid molecule encoding a SSeCKS polypeptide comprising a CY domain that is capable of binding cyclin D and preventing translocation of cyclin D into the nucleus.

14. (amended) The method of claim 13 wherein the nucleic acid molecule further encodes a cytoskeltal anchoring peptide wherein said peptide is linked to the encoded SSeCKS polypeptide.

15. (amended) A method of inhibiting cell proliferation in a cell comprising introducing a nucleic acid molecule encoding a SSeCKS polypeptide that has an increased affinity for cyclin D as compared to a wild type SSeCKS polypeptide.